Treatment of Hypertension

The Special Place of Alpha-Methyldopa—A Short Term Study

MAX H. WEIL, *M.D., Ph.D.*, and BENJAMIN H. BARBOUR, *M.D.*, Los Angeles

• **Alpha-methyldopa in amounts of 750 mg twice daily is an effective antihypertensive agent, intermediate in potency between reserpine-thiazide combinations and ganglionic-sympathetic blocking drugs. Because it produces few undesirable side effects, it is well accepted by patients.**

It is useful for patients with moderate or severe hypertension not controlled by reserpine-thiazide combinations. Its favorable action on cardiac output and renal blood flow provides special advantages for patients with advanced hypertension aggravated by cardiac or renal combinations.

A METHOD by which chemical formation of vasopressor substances would be blocked gives promise of a superior approach to the treatment of arterial hypertension. Alpha-methyldopa,* a decarboxylase inhibitor, is a new antihypertensive drug which acts at least partly in this manner. Its potential clinical value as an antihypertensive drug was first emphasized by Oates and his associates.[6]

Although the mechanism by which this drug produces its hypotensive action is not completely understood, its pharmacological effect is probably due to a reduction in the synthesis of norepinephrine. Unlike most other potent medications currently used for the treatment of hypertensive vascular disease, alpha-methyldopa does not block transmission of autonomic impulses but lowers concentration of norepinephrine and serotonin in the tissues. This mode of action has advantages for it offers selectivity as well as specificity.

Antihypertensive drugs exerting more generalized interference with autonomic functions have discomforting side effects, including constipation, nasal stuffiness, dry mouth, visual disturbances and impotence. These are observed during treatment with rauwolfia alkaloids, ganglionic blocking drugs and postsympathetic blocking drugs, but usually do not occur during treatment with the new drug. More extensive clinical experience reported from various centers, including our own,[1,2,4,5] and a series of studies reported at the International Congress of Cardiology in Mexico City last October by Edwards, Dollery, Bayliss and others, confirm these findings.[3] There was exceptional interest in this drug and no other single subject received such wide attention at this International Congress. Eighteen studies were presented on alpha-methyldopa from 14 different countries on four continents.

*Supplied as Aldomet by Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania.

From the Department of Medicine, University of Southern California School of Medicine and the Los Angeles County Hospital, Los Angeles 90033.

Presented before the Section on Internal Medicine at the 92nd Annual Session of the California Medical Association, Los Angeles, March 23 to 27, 1963.

Supported by The John A. Hartford Foundation, Inc., New York, and Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania.

In assessing the place of alpha-methyldopa as an addition to the already extensive armamentarium of antihypertensive drugs, we examined the clinical, hemodynamic, renal and metabolic changes which followed its use. This antihypertensive agent may have special advantages because, while lowering arterial pressure, it has relatively few unfavorable side effects and does not compromise cardiac or renal function. The method and detailed results of our studies have already been described.[7]

Studies on Hypertensive Patients

Twenty-five patients (12 men and 13 women) in the medical wards of the Los Angeles County Hospital were studied. Each patient had a diastolic pressure of 110 mm of mercury or higher after admission to the hospital. No drugs had been used for the treatment of hypertension for two weeks preceding our study. Detailed information and laboratory data indicated no specific cause of hypertension in 22 of the patients. In two patients hypertension was related to chronic pyelonephritis, and one patient had polycystic kidney disease. The patients were observed for a control period before alpha-methyldopa was given, then for at least ten days of treatment, and for five to thirteen days after treatment was stopped.

After administration of alpha-methyldopa the blood pressure fell in every patient—in the standing as well as in the supine posture. These changes were highly significant for the probability that they could occur by chance is less than one in a thousand ($p > 0.001$). In the five days following discontinu-

ance of the drug a significant reduction of blood pressure persisted. These effects are summarized in Table 1. Postural accentuation of the hypotensive effect in the standing position was prominent.

The effective amount of the levorotatory compound (or its racemic equivalent) ranged from 1.5 to 2.5 gm, administered in two or three divided doses daily; the one patient who received 3.0 gm had excessive postural hypotension. Sedative effects occurred in one-third of the patients but usually subsided by the second day, occasionally not until the third day.

The leukocyte content of the blood, blood urea nitrogen, serum creatinine, blood sugar content (fasting), and serum potassium were not significantly modified by the treatment. The hemoglobin concentration fell in all but three cases. The average change was from 14.1 to 12.7 gm per 100 cc of blood. A 5 gm fall in two patients was associated with increasing renal failure. Liver function tests, including serum bilirubin, bromsulfalein retention, alkaline phosphatase, thymol turbidity and serum transaminase, were not changed.

Hemodynamic and Renal Function Studies

Results of hemodynamic studies are summarized in Table 1. Only a slight decrease in the cardiac index occurred after blood pressure had been lowered. Venous pressure was slightly decreased. Perhaps most important, peripheral vascular resistance was reduced during therapy with alpha-methyldopa.

There was a concomitant reduction in heart rate from 82 to 75 beats per minute; in the work of the heart from 123 to 86 gm M per beat; and in the mean circulation time, measured by indocyanine green dye, from 14.5 to 13.1 seconds. A significant observation was an increase in plasma volume from 3.0 to 3.7 liters, which suggested that dilution was the factor responsible for the lower hemoglobin and hematocrit readings.

Creatinine clearance, a measure of glomerular filtration rate, increased in six of nine patients. In only one instance was a definitive decrease shown. Clearance of para-aminohippurate (PAH), an index of renal blood (plasma) flow, was not significantly altered. Mean values are shown in Table 2. As arterial pressure was reduced, clearance of PAH was unchanged and clearance of creatinine was increased. Serum urea nitrogen and creatinine were stable. The findings, therefore, gave evidence that treatment with alpha-methyldopa does not reduce

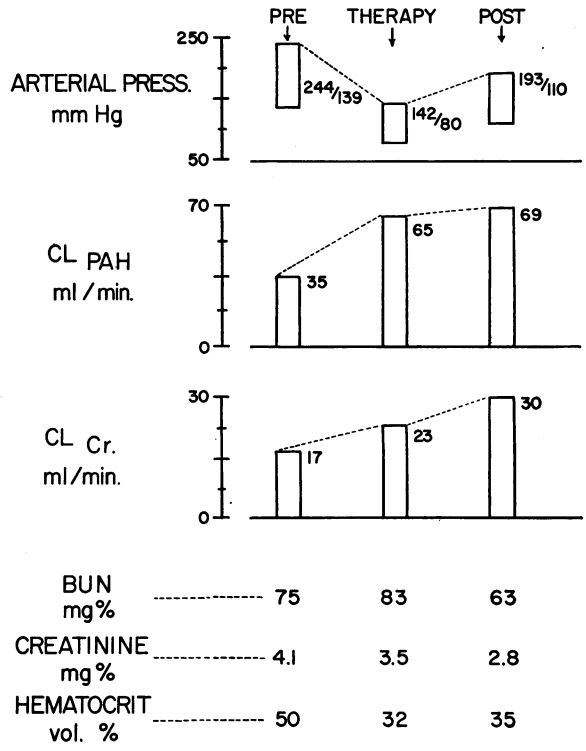

Chart 1.—Renal function during lowering of blood pressure with alpha-methyldopa (250 mg three times a day for ten days) in a 49-year-old woman with severe hypertension complicated by renal failure. CL PAH = para-aminohippurate clearance. CL Cr = creatinine clearance.

TABLE 1.—*Hemodynamic Studies Before and After Treatment with Alpha-Methyldopa*

	Before Treatment	During Treatment
Blood pressure*		
Supine	188/110	151/89
Standing	175/116	123/84
Venous pressure† mm Hg	7	5
Cardiac index† liters per minute per square meter of body area	2.9	2.6
Peripheral resistance† dynes sec.cm^{-5}	2340	1850

*Mean value in 25 patients.
†Mean value in 4 patients.

TABLE 2.—*Renal Function Before, During and After Therapy with Alpha-Methyldopa*

	Number Patients	Normal Range	Before Treatment	Ten Days of Treatment	Five Days After Treatment
Creatinine clearance (ml per minute)	9	90-130	68	91	78
Para-aminohippurate clearance (ml per minute)	9	500-700	382	450	409
Serum urea nitrogen (mg per 100 cc)	25	7-18	24	27	29
Serum creatinine (mg per 100 cc)	8	0.7-1.3	2.0	2.0	1.9

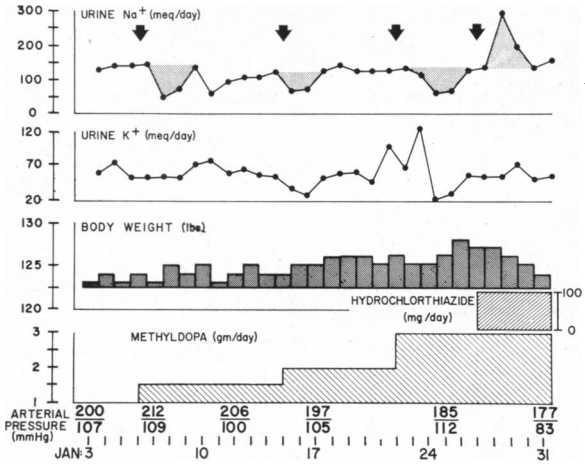

Chart 2.—Metabolic studies demonstrating sodium retention and weight gain with increasing amounts of alpha-methyldopa reversed with hydrochlorothiazide in a 57-year-old man with essential hypertension.

glomerular filtration rate but may result in slightly increased filtration. The index of renal blood flow remained unaltered. From a clinical viewpoint, it is reassuring that alpha-methyldopa did not cause a decrease in creatinine or PAH clearance. In the patient in renal failure (illustrated in Chart 1) reduction in blood pressure from 244/139 to 142/80 mm of mercury was accompanied by improvement in clearance values. No significant elevation of the blood urea nitrogen occurred.

The hypotensive effect was not accompanied by sodium diuresis. To the contrary, treatment in three of four patients was followed by a net retention of sodium and a gain in body weight (Chart 2). Sodium retention was also observed when there was a relatively poor therapeutic response. No symptoms referable to sodium retention were noted by us, but other investigators have reported congestive heart failure as a potential complication of treatment. Metabolic studies in our hospital suggest that this is easily avoided by concomitant use of a thiazide diuretic, which also increases the effectiveness of alpha-methyldopa as an antihypertensive drug. These features are illustrated in Chart 2.

Alpha-methyldopa might prove particularly helpful in the treatment of patients with severe or malignant hypertension and renal failure. It has now been shown by us and by others that in lowering arterial pressure the agent does not significantly alter cardiac output. This is particularly desirable in patients who have vascular complications due to hypertension and arteriosclerosis. Lowering of renal artery pressure and cardiac work is essential, but lowering of cardiac output by use of ganglionic blocking drugs creates risks. Renal and coronary insufficiency are accentuated. Myocardial infarction may occur as an acute complication, and renal failure is accentuated. This risk is minimized if arterial pressure is lowered by lowering peripheral resistance rather than cardiac output.

CLINICAL OBSERVATIONS

Since completion of detailed hemodynamic, renal and metabolic studies, we have had experience in the clinical use of this drug in an additional ten patients. A hypotensive effect usually was first manifest within eight hours after the oral dose was taken. The peak effect occurred between 12 and 24 hours, but occasionally it was delayed for as long as 48 hours. Reduction in blood pressure proceeded gradually. Thus, when administered in adequate doses the drug appeared to "normalize" blood pressure. Excessive or unpredictable hypotensive effects were rarely observed. Postural hypotension occasionally proved troublesome, but rarely so when the patients were forewarned.

The drug was well tolerated and had good patient acceptance. The only side effect consistently observed was sedation to the extent that the patient preferred to remain in bed during the first 24 hours after treatment was begun. We recently observed one patient who had transient abnormalities of liver function, and other investigators have observed fever with associated abnormalities in liver function tests. In no case has permanent injury resulted.

In addition to its antihypertensive action, alpha-methyldopa often has a subtle tranquilizing (and often mood-lifting) effect which patients like. Occasionally quite the opposite is noted and the patient has subjective weakness and malaise. Tolerance to its antihypertensive action has been observed but the effectiveness is often restored by the addition of a thiazide diuretic, such as hydrochlorothiazide. Between 25 and 75 mg of hydrochlorothiazide may be administered along with each dose of alpha-methylodopa.

CURRENT EVALUATION

At this time alpha-methyldopa may be regarded as sufficiently free of toxic effects to justify its clinical use. However, the number of patients we have studied is small and more definitive reassurance would be premature.

Alpha-methyldopa is likely to achieve an important place in the treatment of hypertension if its safety is confirmed in a larger number of patients. It probably ranks with reserpine-thiazide combinations in mildness of side effects, but outranks them in terms of potency. In turn it is outranked in potency by guanethidine and mecamylamine. It may well replace hydralizine, which also

has favorable effects on cardiac and renal function. However, hydralizine is less potent in its antihypertensive action and also is beset by a high incidence of unfavorable side effects.

University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033 (Weil).

ACKNOWLEDGMENTS: The collaborative aid of Dr. Robert Chesne, the technical assistance of Mr. John Barr, and the secretarial aid of Mrs. Marian Snure are gratefully acknowledged.

REFERENCES

1. Barbour, B. H., and Weil, M. H.: Treatment of hypertension with alpha-methyl DOPA, Circulation, 24:880, 1961 (Abstract).

2. Cannon, P. J., Whitlock, R. T., Morris, R. C., Angers, M., and Laragh, J. H.: Effect of alpha-methyl DOPA in severe and malignant hypertension, J.A.M.A., 179:673-681, 1962.

3. Chavez, I.: Abstracts: The Fourth World Congress of Cardiology: The International Society of Cardiology, Mexico City, October 7-13, 1962.

4. Gillespie, L., Jr., Oates, J. A., Crout, J. R., and Sjoerdsma, A.: Clinical and chemical studies with α-methyl dopa in patients with hypertension, Circulation, 25:281-291, 1962.

5. Irvine, R. P., O'Brien, K. P., and North, J. D.: Alpha-methyl DOPA in treatment of hypertension, Lancet, 1:300-303, 1962.

6. Oates, J. A., Gillespie, L., Udenfriend, S., and Sjoerdsma, A.: Decarboxylase inhibition and blood pressure reduction by alpha-methyl-3,4-dihydroxy-DL-phenylalanine, Science, 131:1890-1891, 1960.

7. Weil, M. H., Barbour, B. H., and Chesne, R. B.: Alpha-methyl DOPA for the treatment of hypertension: Clinical and pharmacodynamic studies. Circulation, 28:165-174, August, 1963.